REMARKS

Status of the Claims

Claims 1 and 61-75 are pending and stand rejected in the subject patent application. Claims 1, 61, 66, 68, 73 and 75 are amended with entry of the instant Amendment. Specifically, Claims 1 and 61 are amended to replace the recitation of "malignant cells" or "tumor" with the recitation of "neoplasm." Support for the amendments can be found in the specification, e.g., at page 5, lines 1-3. Claim 1 is also amended to replace "immunizing" with "administering." Support for this amendment can be found in the specification, e.g., at page 7, lines 16-27; and page 37, lines 25-28.

In addition, Claims 1 and 61 are further amended to replace the recitation of "expresses a Her-2/Neu protein" with the recitation of "overexpresses a Her-2/Neu protein." These amendments have support in the specification, e.g., at page 20, line 24. Claims 66 and 73 are amended to specify that the second component is P3CSS. Claims 68 and 75 are amended to specify that "the second polypeptide is TPPAYRPPNAPIL (SEQ ID NO:9)." Support for these amendments is self evident since the amendments merely replace the open-ended term, "comprises," with a close-ended term ("is").

Applicant notes that the claim amendments presented herein do not introduce new matter. Unless otherwise indicated, the amendments have been made to improve clarity or to expedite prosecution of the subject application, and should not be construed as acquiescence of any ground of rejections.

The following remarks address issues raised in the instant Office Action.

Rejections Under 35 U.S.C. § 112, First Paragraph, Written Description

Claims 61-68, 73 and 75 are rejected as allegedly not complying with the written description requirement. The Examiner alleged that there is a lack of written description because the recitation of "a polypeptide having the amino acid sequence VMAGVGSPYV (SEQ ID NO:12)" in Claim 61 encompasses peptides that comprise SEQ ID NO:12. Additional basis of the rejection, as alleged in the Office Action, is the recitation of "comprises" in Claims 66, 68, 73 and 75. The Examiner was of the view that there is a lack of written description for a second component comprising P3CSS (as recited in Claims 66 and 73) and a second polypeptide comprising SEQ ID NO:9 (as recited in Claims 68 and 75).

Applicant respectfully disagrees with the Examiner's assertions and reasoning underlying the instant rejection. However, in order to expedite prosecution of the subject patent application which has already been pending for more than 7 years, Applicant has amended the relevant claims noted above. Specifically, Claim 61 is amended to recite a polypeptide with the amino acid sequence of SEQ ID NO:12. Claims 66 and 73 as presently amended recite that the second component is P3CSS. Similarly, the presently amended Claims 68 and 75 recite that the second polypeptide is the peptide of SEQ ID NO:9. As such, Applicant believes that the Examiner's concerns have all been adequately addressed. Therefore, the instant rejection should be withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1 and 61-75 are rejected as allegedly not enabled. The Examiner acknowledges that the specification enables

methods for activating specific cytotoxic T lymphocytes in vivo in an animal having a breast cancer that overexpresses a Her-2/Neu protein and methods for treating breast cancer that overexpresses a Her-2/Neu protein. However, the Examiner takes the position that the subject disclosure does not enable methods for activating specific CTLs for malignant cells that express a Her2/neu protein or methods of treating any tumor that expresses a Her-2/Neu protein. It is additionally alleged in the Office Action that the methods are not enabled because of the recitation of a polypeptide having SEQ ID NO:12 in Claim 61, the recitation of a second component that comprises P3CSS in Claims 66 and 73, and the recitation of a second polypeptide that comprises SEQ ID NO:9 in Claims 68 and 75.

Applicant respectfully traverses the present rejection for the reasons stated on the record. Nevertheless, in the interest of expediting prosecution of the subject patent application, Applicant has amended the claims in order to address the issues raised by Examiner. Specifically, as noted above, Claims 61, 66, 68, 73 and 75 have been amended to remove any term which the Examiner considers open-ended language with respect to the recitation of SEQ ID NO:12, SEQ ID NO:9 or P3CSS in these claims. In addition, Claims 1 and 61 have been amended to specify that the claimed methods are directed to subject having a neoplasm that overexpresses Her2-Neu. Applicant submits that these amendments have adequately addressed the Examiner's concerns and respectfully requests that the instant rejection be withdrawn.

Rejection under 35 U.S.C. § 102(b)

Claims 1, 61-67 and 69-74 are rejected as allegedly being anticipated by Grey et al., of record (WO 94/20127). The

Examiner took the view that Grey et al. teaches a peptide that is the same as the polypeptide of SEQ ID NO:12 of the subject patent application, and that Grey et al. teaches the use of pharmaceutical compositions comprising such a peptide to treat cancer.

As a initial matter, Applicant notes that the instant rejection appears to have been incorrectly made under 35 U.S.C. § 102(b). This is because Grey et al. was published on September 15, 1994. On the other hand, the subject patent application claims priority to PCT/US95/16415 which in turn claims priority to US patent application 08/355,558, filed December 14, 1994. Thus, the subject patent application has an effective filing date of no later than December 14, 1994, less than one year after the publication date of Grey et al. Therefore, a rejection under 35 U.S.C. § 102(b) is clearly improper. The following remarks are presented to address an anticipation rejection that might have been rendered under 102(a).

Applicant respectfully traverses the rejection for reasons of record and for the reasons stated herein. The presently claimed invention (e.g., Claims 1 and 61) is directed to methods of employing the polypeptide of SEQ ID NO:12 to specifically activate CTLs in an animal having a neoplasm that overexpresses a Her-2/Neu protein or to treat subjects suffering such a neoplasm. Grey et al. may have showed that a peptide with the same sequence of SEQ ID NO:12 ("peptide 1.0738") is able to bind to HLA-A2.1. This reference does not teach the use of such a peptide to specifically activate CTLs in an animal having a neoplasm that overexpresses Her2/Neu. Therefore, Grey et al. cannot anticipate the present invention

because Grey et al. does not teach each and every element of the presently claimed invention.

In addition, Grey et al. does not and could not anticipate the presently claimed invention because it does not contain an enabling disclosure, even assuming for the sake of argument that the reference may have suggested some elements of the present invention. "In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure' ... ." In re Hoeksema, 399 F.2d 269, 158 USPQ 596 (CCPA 1968). See also MPEP § 2121.01. In the instant case, the cited reference merely discusses that peptide 1.0738 (among a number of other peptides) is able to bind to HLA-A2.1 in vitro (at page 51, lines 7-29). There is no actual disclosure or evidence in Grey et al. that this peptide can specifically activate CTLs in an animal. The Examiner is advised that the only experimental data on immunogenicity and CTL-inducing activity of the HLA-A2 binding peptides in Grey et al. relates to peptides derived from HBV polymerase. As indicated in Example 10 (see, page 76, lines 17-30, and Table 24 of Grey et al.), it appears that a total of 13 9-mer peptides from HBV polymerase were examined for activity to induce cytotoxic activity. Specifically, CTLs were isolated from transgenic mice immunized by the peptides and restimulated with lymphoblasts coated with the peptides. The cultured CTLs were then examined for cytotoxic activity on peptide-coated Jurkat A2/kb cells. The results suggest that 5 of the 13 9-mer peptides derived from HBV polymerase are capable of inducing CTLs, as shown in Table 24. Grey et al. further notes that these five peptides all bind to HLA-A2.1 with a relative

binding affinity greater than 0.01. It is then concluded, without additional experimental data or evidence, that "[a]ll of the peptides in Appendices 1 and 2 having a binding [affinity] of at least about 0.01 would be immunogenic" (at page 76, lines 31-34).

Thus, the only discussion in Grey et al. that might be relevant to the present invention relates to the HLA-A2.1-binding activity of the peptides shown in Appendices I and II, the CTL-inducing activities of the peptides derived from HBV polymerase, and the conclusory statement noted above. Applicant submits that such a disclosure does not enable the presently claimed invention. First, Applicant notes that the reasoning underlying the above mentioned conclusion of Grey et al. is logically flawed. Grey et al. showed that all five peptides (out of a total of 13 9-mer peptides derived from HBV polymerase) which were able to induce CTLs have a relative binding affinity greater than 0.01. Even assuming that a sample pool of 5/13 is statistically significant, it at most would lead to a conclusion that all 9-mer HBV polymerase peptides that are immunogenic bind to HLA-A2.1 with a binding affinity of at least 0.01. However, it does not logically follow that any 9-mer HBV polymerase peptide with a binding affinity for HLA-A2.1 that is at least 0.01 is necessarily immunogenic. To the contrary, it is likely that some 9-mer HBV polymerase peptides (let alone 10-mer peptides derived from proteins other than HBV polymerase) which have the noted binding affinity will not induce CTLs. In other words, a binding affinity of at least 0.01 is a necessary, but not sufficient, condition for the peptide to be immunogenic.

In addition, there is clearly a lack of experimental evidence to support the above-noted broad conclusion of Grey et

al. Grey et al. did not examine immunogenicity of the peptides listed in Appendices I and II that are derived from any protein other than HBV polymerase, including any of the c-Erb2 (Her-2/Neu) peptides. Grey et al. also did not examine immunogenicity or CTL-inducing activity of any 10-mer peptides set forth in Appendices II (including 10-mer peptides derived from HBV polymerase). Thus, it is readily apparent that, unlike the subject specification, Grey et al. did not and could not enable the use of the specific 10-mer c-Erb2 peptide ("peptide 1.0738") to activate CTLs in an animal having a neoplasm that overexpresses Her-2/Neu (c-Erb2). Since there is no enabling teaching in the cited reference or in the other prior art that this specific c-Erb2 peptide would be able to activate CTLs in an animal, the presently claimed invention are not anticipated. Accordingly, Applicant respectfully requests that the instant rejection be withdrawn.

Rejection under 35 U.S.C. § 103(b)

Claims 68 and 75 are rejected as allegedly being obvious over Grey et al. in view of US Patent 6,419,931 (Itiello et al.). The Examiner acknowledged that Grey et al. does not teach a T cell helper-inducing peptide with the amino acid sequence of SEQ ID NO:9. The Examiner noted that Itiello et al. discusses a T helper epitope with the same amino acid sequence as SEQ ID NO:9. The Examiner then alleged that it would have been obvious to replace the T helper inducing peptide discussed in Grey et al. with the T helper epitope of Itiello et al. This rejection is respectfully traversed for the reasons stated below.

1. The rejected claims cannot be both non-enabled and obvious

Before specifically addressing the alleged obviousness issue, Applicant first notes that claims 65 and 78 are rejected as both lacking enablement and being obvious. However, this simply cannot be legally and logically correct. The legal relationship between obviousness and enablement is well established. To render an invention "obvious" the prior art as a whole (i.e., all of the references in the prior art, in combination) "must enable one skilled in the art to make and use the apparatus or method," before that apparatus or method can be considered obvious. See Beckman Instruments Inc. v. LKB Produkter AB, 13 USPQ2d 1301, 1304 (Fed. Cir. 1989). The basic question regarding the relationship between enablement and obviousness is whether the prior art is such as to place the invention in the hands of the public, without the benefit of an applicant's disclosure. See, e.g., In re Brown, 141 USPQ 245 (C.C.P.A. 1964), and In re Payne, 606 F.2d 303, 314 (C.C.P.A. 1979) ("References relied upon to support a rejection under 35 U.S.C. § 103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public."). On the other hand, for enablement purposes, an application is considered for what it teaches, in combination with the prior art. Before an application can be non-enabling, the application, in combination with everything that is known in the prior art, must not teach how to practice the invention.

It should be immediately apparent that there is no way that an invention can be both obvious and not enabled. To be obvious, the prior art, without the benefit of an applicant's disclosure, must teach one of skill how to make or use the invention. To be not enabled, the application, in combination with the prior art, must not teach one of skill how to practice

the invention. It is simply impossible for the references cited by the Examiner to teach one to practice the methods of Claims 68 and 75, while the same references plus the subject specification do not. This logical non sequitur has been expressly disapproved by the Federal Circuit. See In re Dow Chemical, 5 USPQ2d 1529, 1531 (Fed Cir. 1988). As indicated by the Federal Circuit in Dow, simultaneously pursuing both arguments demonstrates substitution of a proper obviousness analysis with an "obvious to try" standard, which has been repeatedly rejected by the Board of Appeals and the Federal Circuit.

In summary, Claims 68 and 75 cannot be obvious over the prior art and yet not be enabled by the specification and the art. Reconsideration and/or clarification by the Examiner is respectfully requested.

2. No prima facie case of obviousness has been established

As stated in the MPEP (at §§ 706.02(j) and 2143), there are three basic elements that must be met to establish prima facie obviousness:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

In addition, it must be noted that the suggestion and the reasonable expectation of success must be founded in the prior art, not in Applicant's disclosure. In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991); see also MPEP §§ 706.02(j) and 2143. The Court of Appeals for the Federal Circuit has repeatedly stated the longstanding prohibition against the PTO's use of an applicant's disclosure as a recipe from which to choose references that describe each of the ingredients:

> Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. See, e.g., C.R. Bard, Inc. v. M3 Sys., Inc., 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998) (describing "teaching or suggestion or motivation [to combine]" as an "essential evidentiary component of an obviousness holding"). In re Dembiczak, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). [emphasis added]

The Court stated that "actual evidence" of a motivation to combine references is required, "[t]hat is, the showing must be clear and particular. See, e.g., C.R. Bard, 157 F.3d at 1352, 48 USPQ2d at 1232. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.'" Id. [emphasis added]

Applicant further directs the Examiner's attention to the MPEP § 2143.01. There, it was expressly stated that "the prior art must suggest the desirability of the claimed invention,"

that "fact that references can be combined or modified is not sufficient to establish prima facie obviousness," and that "fact that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish prima facie obviousness" (MPEP, at pages 2100-123 and 2100-124).

Turning to the instant case, it is abundantly clear that a prima facie case of obviousness could not be and has not been established by the Office. First, there is no suggestion or motivation for one to combine the teaching of peptide 1.0738 in Grey et al. with the teaching of T helper peptide in Itiello et al. As noted above, Grey et al. only reports that several 9-mer peptides derived from HBV polymerase are able to induce CTLs. There is no experimental evidence showing immunogenicity of peptides derived from c-Erb2. In addition, Grey et al. specifically suggests that 10-mer peptides bind to HLA-A2.1 with lower affinity than 9-mers. Thus, one would certainly not be motivated to employ the 1.0738 peptide, a 10-mer derived from c-Erb2, in the methods of Itiello et al. The needed motivation would definitely not come from the sheer speculation in Grey et al. that all other peptides that bind to HLA-A2.1 with binding affinity greater than 0.01 may also be immunogenic. To the contrary, one might well be taught away from Claims 68 and 75 since one would expect that a 9-mer peptide derived from HBV polymerase would be better suitable for use in the methods of Itiello et al. For the same reason, one would also not have any reasonable expectation that peptide 1.0738 would be effective in stimulating CTLs along with the T helper peptide of Itiello et al. Finally, the cited references do not teach or suggest all elements of the claimed invention, i.e., using a peptide of SEQ ID NO:12 to specifically activate

CTLs in subjects having a neoplasm that expresses Her-2/Neu. The combined teachings of the cited references do not amount to an enabling disclosure with respect to Claims 68 and 75.

With due respect, Applicant notes that the instant rejection is a typical example of "hindsight-based obviousness analysis." The alleged obviousness stems from nothing but the prohibited hindsight gleaned from the subject disclosure. For all the reasons stated above, Applicant strongly urges that the instant rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, please telephone the undersigned attorney at 858-784-2937.

If there are any additional fees (or overpayments) associated with this Response, or any Response associated with this application, the Director is hereby authorized to charge (or credit) our Deposit Account No. 19-0962.

Respectfully submitted,

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Date

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